AMENDMENT

In the Claims

Please cancel claims 31-34 and amend the remaining claims as follows:

1. (Amended) A method for producing bone *ex vivo*, comprising the steps of:

a) obtaining an osteogenic cell or bone precursor cell;

b) culturing said cell under serum free conditions in the presence of one or more osteogenic growth factors; and

c) maintaining the cell cultures at cell densities that allow the formation of a bone cell spheroid,

whereby bone is formed by cells within said bone cell spheroid.

REMARKS

I. Status of the Claims

Claims 1-38 are pending in the application. Claims 31-37 stand withdrawn. Claims 1-30 and 38 have thus been examined as stand objected to and rejected under 35 U.S.C. §112, first paragraph. The specific grounds for objection/rejection, and applicants' responses thereto, are set out in detail below.

II. Objections

The examiner indicated that certain claims contain minor spelling errors. Applicants have reviewed the claims and provided amendments where appropriate.

III. Rejection of Claims Under 35 U.S.C. §112, First Paragraph

Claims 1-30 and 38 are rejected under the first paragraph of §112 as lacking an enabling disclosure. More specifically, the examiner argues that the specification only enables use of factors that are TGF-β superfamily members. In addition, it is argued that "immediate" culture of cells following obtaining precursors is required. Applicants traverse

Turning first to the issue of "immediate" culturing, applicants believe the examiner has misunderstood the relationship between growth factor culturing, serum conditions, adherence and spheroid formation. As stated at page 12, lines 11-18:

> Under normal culture conditions, osteogenic cells are grown ***in the presence of varying amounts of serum***, and remain adherent to the culture dish, essentially growing as a two dimensional, planar sheet of cells. The *in vitro* expansion of these cells requires their release from the plastic by trypsin treatment and reculturing. After 4 to 6 weeks, the cells are placed ***in media containing serum*** and higher levels of calcium and phosphate. These cells reach confluent densities, and then "pile up" forming multi-layered cell structures referred to as bone nodules that mineralize their surrounding extracellular matrix.

(Emphasis added). From this passage, it should be clear that the undesired adherence, followed by planar sheet and bone nodule formation, occurs in the ***presence*** of serum. The present invention is distinct from this:

> In sharp contrast, osteogenic cells grown ***in serum-free conditions*** undergo a distinctly different developmental pattern resulting in the creation of a new composition of matter. This process requires the presence of TGF-β, or other osteogenic growth factors, added within the first 0 to 48 hours of culture. Under these conditions, the cells become plastic adherent for an additional 24 to 36 hour period; spontaneously release from the plastic surface of the tissue culture dish; form non-adherent variably sized three-dimensional spheroid-shaped cell aggregates, termed "bone cell spheroids."

Specification at page 12, lines 19-25 (emphasis added). Thus, it is not necessary that growth factors be added ***immediately***, but rather, that the culturing take place in the ***absence*** of serum. Clearly, the specification clearly provides the appropriate operative parameters for this method, which are unnecessary in the claims. *Ex parte Jackson*, 218 U.S.P.Q. 804 (CCPA 1982).

Turning to the issue of growth factors, applicants submit that the examiner has not established any reason to doubt applicants' presumptively enabling disclosure. *In re Marzocchi*, 169 UPSQ 370 (CCPA 1971). Rather, the examiner has simply stated, without any support, that "absent a further showing of predictability, it remains unpredictable that any of the multiple and diverse growth factors that may have a growth promoting effect in an accessory nature will be effective in the practice of the claimed invention." Office Action at page 3. This statement indicates that ***applicants*** have the initial burden to come forward with evidence that the scope of their claims is appropriate. However, the cited precedent clearly places the initial burden on the ***examiner*** to rebut applicants' assertions in favor of enablement. The examiner simply has not carried that burden.

In light of the foregoing, applicants respectfully request reconsideration and withdrawal of the rejection.

IV. Conclusion

In light of the foregoing, applicants respectfully submit that all claim are in condition for allowance, and an early notification to that effect is earnestly solicited. The examiner is invited to contact the undersigned at the telephone number listed below with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

Steven L. Highlander
Reg. No. 37,642
Attorney for Applicants

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
(512) 536-3184

Date: January 10, 2003

APPENDIX A: MARKED UP COPY OF AMENDED CLAIMS

1. (Amended) A method for producing bone *ex vivo*, comprising the steps of:

a) obtaining an osteogenic cell or bone precursor cell;

b) culturing said cell under serum free conditions in the presence of one or more osteogenic growth factors; and

c) maintaining the cell cultures at cell densities that allow the formation of a bone cell spheroid,

whereby bone [if] is formed by cells within said bone cell spheroid.

31-34. (Canceled)

APPENDIX B: CLEAN COPY OF PENDING CLAIMS

1. A method for producing bone *ex vivo*, comprising the steps of:

   a) obtaining an osteogenic cell or bone precursor cell;
   b) culturing said cell under serum free conditions in the presence of one or more osteogenic growth factors; and
   c) maintaining the cell cultures at cell densities that allow the formation of a bone cell spheroid,

   whereby bone is formed by cells within said bone cell spheroid.

2. The method of claim 1, wherein the osteogenic cell or bone precursor cell is of human origin.

3. The method of claim 1, wherein the osteogenic cell or bone precursor cell is of bovine origin.

4. The method of claim 1, wherein the osteogenic cell or bone precursor cell is of equine origin.

5. The method of claim 1, wherein the osteogenic cell or bone precursor cell is of canine origin.

6. The method of claim 1, wherein the osteogenic cell or bone precursor cell is of feline origin.

7. The method of claim 1, wherein the osteogenic cell or bone precursor cell is of murine origin.

8. The method of claim 1, wherein the osteogenic cell or bone precursor cell is of rat origin.

9. The method of claim 1, wherein the osteogenic cell or bone precursor cell is of chick origin.

10. The method of claim 1, wherein the growth factor is TGF-β1, TGF-β2, TGF-β1.2, VEGF, insulin-like growth factor I or II, BMP2, BMP4, or BMP7.

11. The method of claim 1, wherein the growth factor is parathyroid hormone, calcitonin, interleukin-6, or interleukin-11.

12. The method of claim 1, further comprising purifying the osteogenic cell or bone precursor cell by physico-chemical separation techniques.

13. The method of claim 12, wherein the physico-chemical separation technique is equilibrium density separation.

14. The method of claim 1, further comprising purifying the osteogenic cell or bone precursor cell by immuno-affinity isolation.

15. The method of claim 14, wherein the immuno-affinity isolation utilizes immune adhesion, immuno-column chromatography, or fluorescence-activated cell sorting.

16. The method of claim 14, wherein the immuno-affinity isolation utilizes antibodies to osteocalcin, osteonectin, or alkaline phosphatase, or combinations thereof.

17. The method of claim 1, wherein said cell-densities at the initiation of the culture are from about 1.0×10^3 to about 1×10^6 cells per cm^2.

18. The method of claim 1, further comprising implanting the cells *in vivo*.

19. A method of providing bone tissue to a mammal, comprising obtaining a bone cell spheroid and implanting the bone cell spheroid into said mammal.

20. The method of claim 19, wherein the bone cell spheroid is implanted in one or more of alginate gels, collagen gels, or fibrin gels.

21. The method of claim 19, wherein the bone cell spheroid is implanted in one or more of polylactic acid, polyglycolic acid or PGLA.

22. The method of claim 19, wherein the bone cell spheroid is implanted in or in conjunction with hydroxyapatitic, other apatitic compounds, devitalized animal bone, devitalized human bone, or porous ceramic structures.

23. The method of claim 19, wherein the implantation is made in conjunction with orthopedic surgery and/or orthopedic devices, such as hip implants, knee implants, or spinal fusions.

24. The method of claim 19, wherein the implantation is made in conjunction with oral surgery and/or dental implants.

25. The method of claim 19, wherein the implantation is made in conjunction with plastic surgery.

26. The method of claim 19, wherein the implantation is in conjunction with periodontal repairs.

27. The method of claim 19, wherein the implantation is into bone-forming tissue.

28. The method of claim 19, wherein the implantation is into a wound.

29. The method of claim 19, wherein the mammal has a bone disease such as osteoporosis, Vitamin D deficiency, Osteotitis deformans, Von Recklinghausen's Disease.

30. A method for producing bone *ex vivo*, comprising the steps of:

a) obtaining an osteogenic cell or bone precursor cell;
b) culturing said cell under serum free conditions in the presence of one or more osteogenic growth factors;
c) maintaining the cell cultures at cell-densities that allow the formation of a bone cell spheroid, whereby bone is formed by cells within said bone cell spheroid; and,
d) removing the cellular elements from the formed bone cell spheroid and using resulting bone *in vivo*.

35. (Withdrawn) A method for identifying a modulator of bone formation, bone repair and/or bone disease, comprising the steps of:

a) obtaining an osteogenic cell or bone precursor cell;
b) culturing said cell under serum free conditions in the presence of a candidate modulator in the absence of one or more osteogenic growth factors;
c) measuring bone cell spheroid formation; and
d) comparing the formation of bone cell spheroid with that observed in the absence of the modulator.

36. (Withdrawn) The method of claim 35, further comprising a step of culturing an osteogenic cell or bone precursor cell in the presence of one or more osteogenic growth factors.

37. (Withdrawn) A method for producing a modulator of bone formation, bone repair and/or bone disease comprising the steps of:

a) obtaining an osteogenic cell or bone precursor cell;

b) culturing said cell under serum free conditions in the presence of a candidate modulator in the presence of one or more osteogenic growth factors;

c) measuring bone cell spheroid formation;

d) comparing the formation of bone cell spheroid with that observed in the absence of the modulator; and

e) producing a modulator so identified.

38. A bone cell spheroid made by the process of:

a) obtaining an osteogenic cell or bone precursor cell;

b) culturing said cell under serum free conditions in the presence of one or more osteogenic growth factors; and

c) maintaining the cell cultures at cell densities that allow the formation of a bone cell spheroid,

whereby bone is formed by cells within said bone cell spheroid.